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EXAMINER
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18M2/0531

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ART UNIT PAPER NUMBER

10

1806

DATE MAILED: 05/31/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/11/94 ☒ This action is made final.
A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-40 are pending in the application.
Of the above, claims 21-27, 30, 31, 35 are withdrawn from consideration.
2. ☐ Claims have been cancelled.
3. ☐ Claims are allowed.
4. ☒ Claims 1-20, 28, 29, 32, 33, 34, 36-40 are rejected.
5. ☐ Claims are objected to.
6. ☐ Claims are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

(Rev. 2/93)

15. Claims currently under consideration are 1-20, 28-29, 32, 33, 34, and 36-40. Claims 21-27, 30-31, and 35 stand withdrawn from consideration. Applicants' request to hold the drawing requirements in abeyance until such time as allowable subject matter is identified is noted. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior office action. The location of this application has changed. All future correspondence regarding this application should be sent to the Examiner's attention with art unit designation 1816. Current fax and telephone contact numbers may be found at the end of this Office Action.
16. Claims 1-8, 11-20, and 36-40 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. or Hirsch et al. ('132), Carriere et al., and Knapp et al. Claims 1-5, 7-8, and 11-16 are drawn to protein-polycation conjugates wherein the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). The claims are also drawn to the use of modified histones, histones, polylysine, protamine in the conjugates as the polycation substance. Claims 17-20 are directed to complexes comprising the conjugates of claim 1 with associated nucleic acids. Claims 36-37 are drawn to a process for the introduction of nucleic acids into T-cells through the use of the conjugates of claim 1. Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells. Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected. Furthermore, Hirsch et al. teach the use (a process of introducing DNA into T-cells) of T-cell specific antibodies to target nucleic acids to T-cells for transformation purposes in order to produce interleukins, etc. (see Example 3). Knapp et al. teach a variety of known T-cell specific antibodies which are commercially available. Carriere teaches that anti-CD4, CD7, and CD5 antibody conjugates are internalized by cells expressing these cell markers (see Abstract and Discussion). CD7 is an admitted tumor associated antigen (see specification, pages 12-13). The substitution of such antibodies as targeting agents of protein-polycation complexes would have been obvious to one of ordinary skill where the targeting of T-cell was desired. Such targeting would be desired when one wished to treat T-cell leukemias or HIV infected T-cells or to induce the production of lymphokines (see

Hirsch). The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells in view of the state of the art and the recognition in the art that the HIV virus was internalized into CD4 expressing cells through the interaction of gp120 with the CD4 molecule. Zon et al is found at page 18 of the specification and is referred to therein as representing known methods of making nucleic acid analogues. This reference also teaches that such analogues are useful for the treatment of HIV infection. Applicants' comments regarding the Carrier (sic) reference are noted. The reference was cited for its teaching that anti-CD4, anti-CD7, and anti-CD5 antibodies were internalized into cells. That the antibodies were bound to gold is immaterial to the issue at hand, however it does provide for teaching that antibody conjugates wherein anti-CD4, anti-CD7, and anti-CD5 antibodies were used as the targeting agents were internalized into cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins. One of ordinary skill in the art would have also been motivated to transfect T-cells through the contacting of T-cell markers with T-cell antibody specific DNA conjugates in o From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons and those set forth in the previous Office Action (see paper #18). Applicant has argues that the rejection oversimplifies the issue. Applicant is respectfully reminded of the test for obviousness. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or

unobviousness.

Scope and Content of the Prior Art: The conjugates of transferrin, polycations, and attached DNA were known before the filing date of the present invention. These conjugates were known to form soluble complexes with DNA and be "adsorbed" into cells (see Wu et al. or Wagner et al.) Applicant is invited to consider paragraph 1, column 2, Wu et al. where it is explicitly taught that the invention is directed to the use of receptor mediated endocytosis to endow cell specificity to gene delivery. The Wu invention uses a ligand-polycation-DNA complex to achieve such delivery. Wagner teaches the use of transferrin-polycation-DNA complexes to transfect cells, and while limited to "transferrinfection" teaches that protein-polycation-DNA complexes were useful for the delivery of DNA into cells. The use of antibodies to deliver DNA and toxin into cells was well established at the time the invention was filed Goers et al. Carriere taught that anti-CD4, anti-CD7, and anti-CD5 antibodies were internalized into cells. At issue is whether the routineer would have recognized that another "targeting" agent, such as an antibody known to be internalized into cells, would have been useful for the direction of DNA into cells and whether such a routineer would have been motivated to substitute such an antibody for the transferrin molecules of the prior art. The primary references differ from the claimed invention in only the targeting agent used to direct the DNA into a cell. One of ordinary skill in the art would have recognized that a molecule which caused internalization of a bound ligand would have been useful as a targeting component of a conjugate comprising a protein-polycation conjugate which are capable of forming soluble complexes with nucleic acids and which are also adsorbed into cells.

As the CCPA stated in the decision In re Payne, 203 USPQ 245 (CCPA 1979), the court held that if two compounds are known to be analogous for a given function, that knowledge is sufficient motivation for substituting one compound for the other. Under the facts of the current situation, both transferrin and anti-CD4, anti-CD7, and anti-CD5 antibodies were recognized to be internalized into cells. Thus, one of ordinary skill in the art would have been motivated to use such targeting agents to delivery nucleotides into cells where such targeting agents were a component of a protein-polynucleotide conjugate capable of forming soluble complexes with DNA and being internalized into cells.

18. Claims 17, 20, 28-29 and 32-34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al., Hirsch et al. ('132), Knapp et al., and Carriere et al., as applied above and further in view of Haseloff et al., or Rossi et al. ('019) and Applicants' admitted prior art regarding oncogene inhibitory nucleic acids (see page 26, paragraph 3 of the specification). The teachings of the Wu et al. (AC1), Wagner et al. (AT2), Goers et al., and Hirsch et al. ('132) references have been discussed above. Claims 28-29 and 33-34 are drawn to protein-polycation/nucleic acid complexes wherein the nucleic acid

is a ribozyme which an inhibitory nucleic acid or an oncogene inhibitory nucleic acid and the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). Wu and Wagner differ from the claimed invention in that the use of antibody targeting agents and nucleic acids comprising ribozymes are not taught. Therapeutic agents of the gene therapy category also include ribozymes. Haseloff et al. teach ribozyme enzymes (ribozymes) and a variety of applications for these molecules (see pages 590-591) such as the specific targeting of a particular gene RNA transcript with ribozymes. The "anti-gene activity" of ribozymes is indicated to provide a basis for gene therapy of various diseases, including HIV infection (column 1, '019). This section also indicates that transfection or transformation techniques to introduce genes encoding ribozymes into various types of cells were known in the art in 1988. Those skilled in the art would have been able to insert ribozymes into a variety of genetic constructs in order to facilitate the expression of the ribozyme of a desired specificity. Rossi et al. teach ribozymes capable of cleaving HIV-1 RNA and provide a variety of therapeutic applications for the disclosed ribozymes of their invention. Included in this teaching is that therapeutic ribozymes may be introduced into cells by a variety of methods including the transfection of cells with DNA encoding the ribozymes of a desired specificity (see column 6, Therapeutic Procedures). Ribozymes are also taught to be capable of inactivating endogenous RNA transcripts including those produced by the ras, myc, or src oncogenes. Ribozyme contained within tRNA transcripts are known in the art (see specification, page 19). In view of the teachings of Rossi et al. and/or Haseloff et al., one of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates such as those taught by Wagner et al. would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that the targeting specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained within the cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the

references, especially in the absence of evidence to the contrary.

19. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons, those set forth in paragraph 17 herein, and those set forth in the previous Office Action (see paper #18). Applicants' traversal covers, essentially, the same ground as that in the previous traversal on the first 103 rejection set forth by the Examiner. Applicants' arguments have been considered but are not found persuasive for the following reasons: This invention substitutes antibodies which are internalized into cells for the transferrin molecule of the prior art as the means for the targeting of nucleic acids into cells. Applicant argues that there is no motivation to target ribozymes to T-cells based on the combination of references. The obviousness of the targeting agent-polycation conjugates have been discussed above. This rejection is based upon the additional element of ribozymes being recited in the claims. Ribozymes are a nucleic acid and one skilled in the art would have expected such ribozymes to be capable of association with the polycation-targeting agent conjugates produced in the previous rejection through the combination of references. One of ordinary skill in the art would have had a reasonable expectation of success in forming a protein (antibody)-polycation-ribozyme complex in view of the combination of references.

NEW GROUNDS OF REJECTION

20. Claims 1 and 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Calliere et al., as applied above (see paragraph 18) and further in view of Goding et al. Claims 1 and 9-10 are drawn to compositions comprising antibodies bound to polycations through protein A antibody interactions. The teachings of the references have been discussed in paragraph 18 and differ from the claimed invention in that the binding attachment of polycation to antibody through a protein A-antibody interaction is not taught in the combination of references. Goding et al. teach that protein A may be used as an immunological reagent for the attachment of reagents to antibody molecules. Specifically, the attachment of labels such as fluorescein or radioisotopes to cell bound antibodies is taught by the reference (see page 248). In view of the art recognition that labels such as fluorescein or radioisotope could be, and were, attached to antibodies through a protein A-antibody interaction, it would have been obvious to one of ordinary skill in the art that polycations could also be attached to antibodies through the protein A-antibody interaction, thereby providing a means of attaching DNA to antibodies or facilitate the isolation of antibodies through ion exchange chromatography.

One of ordinary skill in the art at the time the invention was made would have been motivated to select make an antibody-protein A-polycation compound because such

proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Applicant traverses on the grounds that the Examiner has utilized improper hindsight to reject the claims. The arguments has not been found persuasive for the reasons cited above and because one of ordinary skill in the art would have recognized that Protein A-polycation conjugates would have been an "universal" reagent useful for the attachment of DNA to IgG antibodies of any specificity. Indeed the art, in addition to Goding et al., had used such conjugates for the delivery of toxins to cells (see Ghetie et al. or Mora et al.). Applicants' arguments have not been found persuasive.
22. No claim is allowed. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

This application may be subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, if this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192.

THIS APPLICATION IS SUBJECT TO PUBLIC LAW 103-465. Therefore, upon the timely filing of a first submission and the appropriate fee of \$750 for a large or ½

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that amount for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

23. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.
24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Eisenschenk whose telephone number is (703) 308-0452. The examiner can normally be reached Monday through Thursday from 6:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone number for Group 180 is (703) 305-3014 or (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.



December 6, 1996
Christopher Eisenschenk, Ph.D.
Primary Examiner
Group 1800